

# EXHIBIT 17



09548 SEP 26 PM 1:49

September 26, 2008

**VIA HAND DELIVERY**

Dockets Management Branch, HFA-305  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**CITIZEN PETITION**

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva")<sup>1</sup> hereby submits this Citizen Petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355(b) and (j)) and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs not approve or accept for filing any abbreviated new drug application ("ANDA") or 505(b)(2) application for a purported generic version or other pharmaceutical alternative to Copaxone® (glatiramer acetate injection) unless and until the applicant satisfies all conditions set forth in this petition. Teva is the manufacturer and distributor of Copaxone®, a treatment for the reduction of relapses in relapsing-remitting multiple sclerosis ("RRMS").

---

<sup>1</sup> Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production and marketing of generic and proprietary branded pharmaceuticals and active pharmaceutical ingredients. Teva is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Neuroscience is the branded neurological products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration and marketing for Teva's branded neurological products in North America, including Copaxone®.

FDA-2008-P-0529

901 E. 104th Street, Suite 900 • Kansas City, MO 64131  
Phone: (800) 221-4026 • Fax: (816) 508-5016

Cl

**I. Actions Requested**

Teva requests that FDA neither approve nor accept for filing any ANDA or 505(b)(2) application that cites Copaxone® as the reference listed drug ("RLD"), or assign an "AB" therapeutic equivalence rating to any purported generic version of Copaxone®, because the clinically active polypeptide sequences in Copaxone® (glatiramer acetate injection) have not been sufficiently well defined to enable an ANDA or 505(b)(2) applicant to conclusively demonstrate that the clinically active polypeptide sequences in its purported generic product are qualitatively and quantitatively "the same as" those in Copaxone®.

In the event that FDA does accept for filing an ANDA that cites Copaxone® as the reference listed drug ("RLD"), Teva requests that any such ANDA be converted to a 505(b)(2) application, and that FDA not approve any such application for a follow-on glatiramoid product, including glatiramer acetate, unless the applicant conducts clinical safety and efficacy studies which are adequately powered and of sufficient duration to conclusively demonstrate that the product is safe and effective. No such product may be assigned an "AB" therapeutic equivalence rating.

A full statement of the grounds justifying these requested actions is set forth below.

## II. Background

### A. Multiple Sclerosis

Multiple Sclerosis (“MS”) is a progressive, immune-mediated disorder that affects the central nervous system (“CNS”). MS is the most common, non-traumatic, disabling neurological disorder in young adults. Approximately 400,000 Americans have MS, and every week about 200 more Americans are diagnosed with the disease. Worldwide, MS affects approximately 2.5 million individuals.<sup>2</sup> Diagnosis typically occurs between the ages of 20 and 40 years, and women are twice as likely as men to develop the disease. Although its etiology is unknown, MS may be triggered in genetically susceptible people by environmental factors.<sup>3</sup>

In MS, inflammatory cells attack myelin, a fatty tissue that surrounds and protects nerve fibers in the brain, spinal cord, and optic nerves. Myelin is lost in multiple areas of the CNS, leaving scar tissue called scleroses (more commonly referred to as lesions). When myelin (or the nerve fiber) is damaged or destroyed, the ability of the nerves to conduct electrical impulses to and from the brain is disrupted, producing the various symptoms of MS.<sup>4</sup>

---

<sup>2</sup> [www.nationalmssociety.org](http://www.nationalmssociety.org).

<sup>3</sup> Bjartmar C, Fox RJ. Pathological mechanisms and disease progression of multiple sclerosis: Therapeutic implications. *Drugs Today* 2002;38(1):17-29.

<sup>4</sup> Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *New Engl J Med* 2000;343(18):938-52.

MS is an unpredictable disease with considerable pathologic heterogeneity. Four different courses of MS have been defined<sup>5</sup>:

***Relapsing-remitting (RRMS).*** People with relapsing-remitting MS experience acute attacks (also called relapses or exacerbations) of neurological dysfunction that can last days or weeks. Following these attacks, patients experience remission periods during which symptoms may lessen dramatically or disappear completely before returning. RRMS is the most common course of MS, occurring in approximately 80% of MS patients.<sup>6</sup>

***Primary-progressive (PPMS).*** This form of MS occurs in 10% to 20% of patients and is characterized by symptoms that progressively worsen over time. There are generally no remissions, though symptoms might temporarily improve.

***Secondary-progressive (SPMS).*** For many patients, MS initially follows a relapsing-remitting course that, over time, changes to a primary-progressive course. Within 5 to 15 years of diagnosis, most RRMS patients (~70%) develop SPMS.

***Progressive-relapsing (PRMS).*** A small percentage of MS patients experience this course, characterized by progressively worsening symptoms and accompanied by acute attacks.

MS is a complicated disease to diagnose because its symptoms are not specific to the disease; many symptoms are common to other diseases as well. Early symptoms include sensory disturbances, weakness, generalized fatigue, visual blurring, and dizziness. Cognitive impairment, depression, vertigo, sensory loss, sexual dysfunction, pain, and spasticity can develop. Symptoms can occur in any combination and can range from mild to severe. As the disease progresses, symptoms worsen and neurologic disability increases; 50% of patients are

---

<sup>5</sup> Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis. *Neurology* 1996;46:907-11.

<sup>6</sup> Noseworthy *et al* (2000).

unable to walk unassisted within 10 to 15 years of an RRMS diagnosis, and after 25 years, 50% are wheelchair-bound.<sup>7</sup>

## **B. Treatment Of MS With Copaxone®**

### **1. Development Of Copaxone®**

Teva manufactures and holds the approved New Drug Application (“NDA”) for Copaxone® (glatiramer acetate injection). Originally known as “Copolymer-1” or “Cop-1,” glatiramer acetate was discovered in the 1960s by Israeli scientists at the Weizmann Institute. Initially, these scientists did not intend glatiramer acetate to *cure* MS; to the contrary, they set out to develop a synthetic copolymer that would mimic myelin basic protein (“MBP”), a central nervous system autoantigen which can induce antibodies that *cause* autoimmune inflammatory destruction of myelin in the brain and *induce* the MS-like disease known as experimental autoimmune/allergic encephalomyelitis (or “EAE”) in animals. Their experiments with glatiramer acetate were unsuccessful: Copolymer-1 not only *failed to induce* EAE—it *prevented* animals from developing the disease.<sup>8,9</sup> Copaxone®’s potential as a treatment for patients suffering from MS was quickly recognized.

---

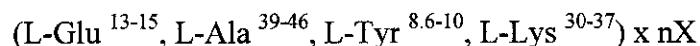
<sup>7</sup> Weinshenker BG. The natural history of multiple sclerosis. *Mult Scler* 1995;13:119-44.

<sup>8</sup> Keith AB, Arnon R, Teitelbaum D, Caspary EA, Wisniewski HM. The effect of Cop-1, a synthetic polypeptide, on chronic relapsing experimental allergic encephalomyelitis in guinea pigs. *J Neurol Sci* 1979;42:267-74.

<sup>9</sup> Teitelbaum D, Webb C, Bree M, Meshorer A, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis in rhesus monkeys by a synthetic basic copolymer. *Clin Immunol Immunopathol* 1974;3:256-62.

## 2. Characterization Of Copaxone®

Glatiramer acetate is a member of the glatiramoid class and is the acetate salt of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine. Glatiramoids are poly( $\alpha$ -amino acids) prepared from N-carboxy- $\alpha$ -amino acid anhydrides. The polymerization occurs through the growth of chains by reaction only with monomers and not with each other. The glatiramoid class of products shares the same relative content of amino acids as glatiramer acetate and is characterized as follows:



(where X represents an anion such as acetate or other pharmaceutically acceptable salt, and the superscripts represent the relative mole percentages of amino acids).

Glatiramer acetate is further defined by the following characteristics which include, but are not limited to: (1) a specific molecular weight distribution profile; (2) complex reproducible patterns in its amino acid sequences; (3) a characteristic ratio of molecules with C-terminal carboxylates to diethylamides; (4) a characteristic electrophoretic profile; (5) specific hydrophobic interactions due to unique charge dispersion; (6) a specific proteolytic digestion profile; (7) a specific affinity to glatiramer acetate antibodies; and (8) a specific potency as determined by its biorecognition by glatiramer acetate-specific T cells.

Although glatiramer acetate has the above characteristics, it has not been fully characterized. Because the glatiramer acetate in Copaxone® is not a single molecular entity, but rather a heterogenous polypeptide mixture that contains a huge, perhaps incalculable number of

active amino acid sequences (“epitopes”) in a defined range of molar ratios, FDA has long recognized that “Copolymer-1 [Copaxone®] is not a conventional drug, either in chemical composition or in its presumed mechanism of action.” *Letter from Paul Leber, MD (former Director, Division of Neuropharmacological Drug Products) to Bruce F. Mackler, PhD, JD*, Dec. 10, 1992.

### **3. Mechanism of Action of Copaxone®**

The precise mechanisms by which Copaxone® product exerts its pharmacological effects in patients with MS are not fully elucidated but the drug is presumed to act as an immunomodulator of the patient’s immune system. Upon subcutaneous injection, Copaxone® degrades into smaller peptides and free amino acids locally, resulting in low or undetectable serum concentrations of the drug or its metabolites. Results of pharmacokinetic (“PK”) studies in healthy volunteers indicate that a substantial fraction of the glatiramer acetate dose is hydrolyzed locally. One immunologic mechanism thought to be central to Copaxone® efficacy is the induction of glatiramer acetate-specific TH2 cells in the periphery, which can cross the blood-brain barrier and directly and indirectly down regulate inflammation within the CNS.<sup>10</sup> However, this may not be the only immunologic mechanism activated by Copaxone®, as evidenced by its induction of various circulating antibodies and effects on other immune cells

---

<sup>10</sup> Aharoni R, Kayhan B, Eilam R, Sela M, Arnon R. Glatiramer acetate specific T cells in the brain express T helper 2/3 cytokines and brain-derived neurotrophic factor in situ. *Proc Natl Acad Sci USA* 2003;100(24):14157-62.

(e.g., monocytes, macrophages, microglia).<sup>11</sup> Moreover, glatiramer acetate need not be in the systemic circulation to exert pharmacodynamic (“PD”) anti-inflammatory effects. Studies in mice show that the drug’s immunomodulating activity can be adoptively transferred to recipient mice by glatiramer acetate-specific T-cells, and not by the drug or by the serum.<sup>12</sup> Thus, there is no PK/PD correlation (i.e., no quantifiable relationship between plasma glatiramer acetate levels and drug efficacy). Consequently, the “sameness” of a purported generic glatiramer acetate product to Copaxone® cannot be demonstrated by means of bioequivalence testing or the use of PD markers.

While Copaxone® is believed to act by modifying immune processes thought to be involved in the pathogenesis of MS, its precise mechanism(s) of action remain unknown and the drug has not been (and, given the limitations of current analytical chemistry techniques—including multidimensional analysis—cannot be) fully characterized. Certain immunologic mechanisms thought to contribute to the positive clinical effects of Copaxone® include<sup>13,14,15</sup>:

---

<sup>11</sup> Ziemssen & Schrempf (2007).

<sup>12</sup> Aharoni R, Teitelbaum D, Sela M, Arnon R. Copolymer 1 induces T cells of the T helper type 2 that crossreact with myelin basic protein and suppress experimental autoimmune encephalomyelitis. *Proc Nat Acad Sci USA* 1997;94:10821-10826.

<sup>13</sup> Ziemssen T, Schrempf W. Glatiramer acetate mechanism of action in multiple sclerosis. *Int Rev Neurobiol* 2007;79:537-70.

<sup>14</sup> Yong VW. Differential mechanisms of action of interferon-β and glatiramer acetate in MS. *Neurology* 2002;59:802-8.

<sup>15</sup> Dhib-Jalbut S. Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. *Neurology* 2002;58(8 Suppl 4):S3-S9.

- High-affinity binding to the major histocompatibility complex (“MHC”), leading to competition with myelin basic protein (“MBP”) at the antigen-presenting cell (“APC”) level for binding to MHC.
- Inhibition of MBP-specific T-cell activation through competition with MBP/MHC complexes for the T-cell receptor, resulting in clonal anergy and deletion of myelin-antigen specific T cells.
- Induction and activation of glatiramer acetate-reactive T cells and a shift in glatiramer acetate-reactive T cells from a dominant type-1 T helper (“TH1”) phenotype, which tends to promote inflammation, to a dominant type-2 (“TH2”) phenotype, which typically promotes an anti-inflammatory environment.
- Preferential migration of glatiramer acetate-reactive TH2 cells into the CNS causes decreased local inflammation through “bystander suppression” (i.e., these TH2 cells release anti-inflammatory mediators upon activation by myelin antigens within the CNS).
- Neuronal and axonal protection related to glatiramer acetate-stimulated secretion of neurotrophic factors, including brain-derived neurotrophic factor (“BDNF”), an important factor for neuronal survival, neurotransmitter release, and dendritic growth.

Continued uncertainty over the drug’s precise mechanism(s) of action precludes a determination of which individual components and sequences of Copaxone®’s polypeptide mixture are most responsible for the product’s clinical efficacy. In fact, due to the enormous number of distinct clinically active polypeptide sequences in Copaxone®, and given the limitations of current analytical chemistry techniques including multidimensional analysis, the active chemical epitopes in glatiramer acetate cannot be identified or characterized. Indeed, given the extraordinary complexity of the immune system itself and the inherent diversity seen in the immune systems of MS patients with unique genetic backgrounds, the widespread biological and clinical efficacy of Copaxone® may be directly related to its heterogenous character, and the drug’s multi-epitopal nature may be the source of its biological and clinical activity.

In contrast to other immunomodulators used in MS, which exert effects in antigen-nonspecific ways, Copaxone® appears to preferentially affect immune cells in an antigen-specific way. Copaxone®, administered subcutaneously daily over many years, works as an antigen-based vaccine. Indeed, Copaxone® has been called “*one of the few practical examples of therapeutic vaccination, as distinct from prophylactic vaccination against infectious disease.*”<sup>16</sup> As early as 1 month after beginning Copaxone® treatment, there is robust proliferation of glatiramer acetate-reactive T cells with a TH2-biased phenotype. After several months of treatment, glatiramer acetate-reactive T cell proliferation declines. Despite the decline, during long-term treatment, there is no decrease in magnitude of cross-reactivity between glatiramer acetate-reactive T cells and MBP, and the cytokines released by glatiramer acetate-reactive T cells remain TH2-biased.<sup>17</sup> Since T cells responsive to myelin antigen epitopes and glatiramer acetate-reactive T cells appear to represent the same or overlapping T cell populations, long-term chronic administration of glatiramer acetate may restore immunologic tolerance in MS patients by sustained deletion of, or anergy induced toward, myelin-antigen-specific T cells.<sup>18,19</sup>

---

<sup>16</sup> Ziemssen & Schrempf (2007).

<sup>17</sup> Chen M, Conway K, Johnson KP, Martin R, Dhib-Jalbut S. Sustained immunological effects of glatiramer acetate in patients with multiple sclerosis treated for over 6 years. *J Neurol Sci* 2002;201:71-7.

<sup>18</sup> Ragheb S, Abramczyk S, Lisak D, Lisak R. Long-term therapy with glatiramer acetate in multiple sclerosis: effect on T cells. *Mult Scler* 2001;7:43-47.

<sup>19</sup> Chen *et al* (2002).

Recent research shows Copaxone® also increases proliferation of glatiramer acetate-specific CD8+ suppressor T cells and regulatory CD4+CD25+ T cells in MS patients.<sup>20,21</sup> Daily immunization with Copaxone® appears to be important for the induction and maintenance of these regulatory and/or suppressive immune cell populations.<sup>22</sup>

In addition to its effect on cellular immunity, glatiramer acetate also exerts effects on humoral immunity. Like vaccines, glatiramer acetate induces the formation of circulating anti-glatiramer acetate-specific antibodies.<sup>23,24,25,26</sup> Studies conducted in RRMS patients demonstrate anti-glatiramer acetate antibody levels peak between 3 and 6 months of treatment then gradually decline but remain above baseline levels.<sup>27,28</sup> Pre-clinical and clinical studies have evaluated the

---

<sup>20</sup> Karandikar NJ, Crawford MP, Yan X, et al. Glatiramer acetate (Copaxone) therapy induced CD8(+) T cell responses in patients with multiple sclerosis. *J Clin Invest* 2002;109:641-9.

<sup>21</sup> Hong J, Li N, Zhang X, et al. Induction of CD4+CD25+ regulatory T cells by copolymer-1 through activation of transcription factor Foxp3. *Proc Natl Acad Sci USA* 2005;102:6449-6454.

<sup>22</sup> Ziemssen & Schrempf (2007).

<sup>23</sup> Brenner T, Arnon R, Sela M, Abramsky O, Meiner Z, Riven-Kreitman R, Tarcik N, Teitelbaum D. Humoral and cellular immune responses to copolymer 1 in multiple sclerosis patients treated with Copaxone. *J Neuroimmunol* 2001;115:152-160.

<sup>24</sup> Farina C, Vargas V, Heydari N, Kumpfel T, Meinl E, Hohlfeld R. Treatment with glatiramer acetate induces specific IgG4 antibodies in multiple sclerosis. *J Neuroimmunol* 2002;123:188-92.

<sup>25</sup> Basile E, Gibbs E, Aziz T, Oger J. During 3 years treatment of primary progressive multiple sclerosis with glatiramer acetate, specific antibodies switch from IgG1 to IgG4. *J Neuroimmunol* 2006;177:161-166.

<sup>26</sup> Teitelbaum D, Brenner T, Abramsky O, Aharoni R, Sela M, Arnon R. Antibodies to glatiramer acetate do not interfere with its biological functions and therapeutic efficacy. *Mult Scler* 2003;9:592-599.

<sup>27</sup> Brenner et al (2001).

effect of glatiramer acetate-reactive antibodies on the biological activity and clinical efficacy of Copaxone®.<sup>29,30</sup> All available data support the conclusion that glatiramer acetate-specific antibodies do not have neutralizing activity. Additionally, no correlation has been found between anti-glatiramer acetate antibodies and the development of local or systemic adverse effects in RRMS patients.

In short, Copaxone®'s complexity and clinical effects distinguish it from typical small molecule drug products.

#### **4. Consistency And Reproducibility Of Copaxone®**

Given the complexity of the glatiramer acetate in Copaxone®, including the huge, perhaps incalculable number of variable patterns in its amino acid sequences, even the most state-of-the-art analytical techniques have not been able to fully characterize the pharmacologically active amino acid sequences within Copaxone®'s polypeptide mixture. As a result, Teva has spent decades studying the correlations among Copaxone®'s chemical, immunological, and biological properties. These studies have led Teva to design and implement a series of well-controlled manufacturing processes and rigorous testing procedures—developed specifically for glatiramer acetate analysis—to ensure the batch-to-batch consistency, safety, and efficacy of the glatiramer acetate in Copaxone®.

---

<sup>28</sup> Teitelbaum *et al* (2003).

<sup>29</sup> Brenner *et al* (2001).

<sup>30</sup> Teitelbaum *et al* (2003)

To that end, proprietary chemical-characterization tests provide crucial information regarding the consistency of Copaxone®'s batch-to-batch production, as well as its quality and stability. Proprietary immunological and biological tests—both *in vitro* and *in vivo*—and other characterization tests are used to demonstrate: (1) the consistency of the antigenic determinants in Copaxone® in order to ensure the reproducibility of the drug's chemical, biological, and immunological properties on a batch-to-batch basis; and (2) the stability of the drug's activity over time. FDA itself long has recognized the importance of these product-specific tests, and required Teva to prove consistency among the multiple Copaxone® batches used in Teva's clinical studies before approving Teva's Copaxone® NDA. Finally, Teva continues to develop new assays and methods to assure the quality of each Copaxone® batch and consistency between Copaxone® batches as well as for research purposes.

## 5. Effectiveness Of Copaxone®

Substantial evidence indicates that Copaxone® has both anti-inflammatory and neuroprotective effects in patients with MS.<sup>31</sup> Extensive clinical experience in RRMS patients has demonstrated the beneficial effects and safety of Copaxone® on the clinical indices of MS—relapse rate and progression of disability—as measured by the Expanded Disability Status Scale (“EDSS”). In a pivotal, double-blind, randomized clinical trial in RRMS patients, relapse rates in patients receiving Copaxone® were approximately one-third lower than rates in patients

---

<sup>31</sup> Ziemssen & Schrempf (2007).

receiving a placebo.<sup>32,33</sup> Similarly, fewer patients receiving Copaxone® experienced sustained disease progression, as measured by the EDSS, than patients receiving placebo.<sup>9</sup> Magnetic resonance imaging (“MRI”) scans<sup>34</sup> of the brain show that treatment reduces the number of enhancing lesions, decreases lesion load, inhibits new lesions from developing into permanent “black holes” (areas of severe and permanent tissue damage), and reduces brain atrophy.<sup>35,36,37,38</sup> Finally, studies show that Copaxone®’s efficacy and safety are sustained over long-term use (>12 years).<sup>39,40</sup>

---

<sup>32</sup> Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995;45:1268-76.

<sup>33</sup> Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate is well-tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. *Neurology* 1998;50:701-8.

<sup>34</sup> Note: there is a modest correlation between MRI findings and clinical evolution of disease; to date there are no established MRI surrogate markers of clinical efficacy and no accepted methods to establish surrogacy.

<sup>35</sup> Comi G, Filippi M, Wolinsky JS, European/Canadian Glatiramer Acetate Study Group. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging—measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* 2001;49:290-7.

<sup>36</sup> Filippi M, Rovaris M, Rocca MA, et al. Glatiramer acetate reduces the proportion of new MS lesions evolving into “black holes”. *Neurology* 2001;57:731-3.

<sup>37</sup> Wolinsky JS, Comi G, Filippi M, et al. Copaxone’s effect on MRI-monitored disease in relapsing MS is reproducible and sustained. *Neurology* 2002;59:1284-6.

<sup>38</sup> Sormani MP, Rovaris M, Valsasina P, Wolinsky JS, Comi G, Filippi M. Measurement error of two different techniques for brain atrophy assessment in multiple sclerosis. *Neurology* 2004;62:1432-4.

<sup>39</sup> Ford C, Johnson K, Brooks B, et al. Sustained efficacy and tolerability of glatiramer acetate in relapsing-remitting multiple sclerosis patients for over 10 years. Proceedings of the 19<sup>th</sup> Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Milan, Italy;2003:Poster 485.

<sup>40</sup> Data on file, Teva Neuroscience Inc.

## 6. Failed Efforts To Modify Copaxone®

In an effort to extend its success with glatiramer acetate, Teva has pursued the development of other products within the glatiramoid class. For instance, Teva scientists developed another glatiramoid product known as TV-5010, or “protiramer” (proposed United States Adopted Name, USAN). Like glatiramer acetate, TV-5010 was a synthetic polypeptide mixture containing the same four naturally occurring amino acids as glatiramer acetate: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine. However, TV-5010 exhibited a modestly higher molecular weight distribution than glatiramer acetate, and was developed by making slight changes to the glatiramer acetate manufacturing process following the polymerization reaction.

The resulting modest increase in TV-5010’s molecular weight significantly increased the product’s immunoreactivity, prompting Teva to undertake a series of pre-clinical chronic toxicity tests on TV-5010 (including tests for genotoxicity, safety pharmacology, chronic toxicity, and reproduction toxicity).<sup>41</sup> The administration of TV-5010 in pre-clinical tests resulted in severe injection site lesions and disseminated necrosis and inflammation of multiple dermal structures, including muscles, nerves, and blood vessels. Chronic treatment led to systemic toxicity, and caused extensive fibrosis, organ damage, eosinophilia, and death. These toxic signs have never been observed in similar pre-clinical studies involving lower molecular weight glatiramer acetate. Notably, some of these toxic effects only became apparent after more than 3 months of chronic TV-5010 administration. As soon as these results became clear, Teva ceased developing

---

<sup>41</sup> Data on file, Teva Neuroscience Inc.

TV-5010. Subsequent physicochemical, biological, and immunological studies confirmed that TV-5010 had a completely distinct immunoreactive and toxicological profile from glatiramer acetate despite only modest changes in its molecular weight distribution.

Teva's experience with TV-5010 demonstrates that even the most minor changes in the manufacturing of glatiramer acetate—and in the molecular weight distribution of the resulting product—will produce a new molecular entity (“NME”) with a significantly different potency and safety and efficacy profile.

### **C. Legal Requirements**

Section 505(j)(2)(A)(ii)(I) of the FDCA (21 U.S.C. § 355(j)(2)(A)(ii)(I)) states that ANDAs must provide “information to show that the active ingredient of the new drug is *the same as* that of the listed drug” (emphasis added). This is commonly called the “sameness” requirement. FDA regulations further provide that “the term ‘same as’ means *identical* in active ingredient(s), dosage form, strength, route of administration, and conditions of use.” *See* 21 C.F.R. § 314.92(a)(1) (emphasis added). Thus, unless an ANDA for a purported generic glatiramer acetate drug product proves that it contains the “same” active amino acid sequences as Copaxone®, FDA may not approve the ANDA, and the ANDA’s sponsor can secure approval for its drug product only by providing clinical data that demonstrate the new drug’s safety and effectiveness as part of the NDA process. 21 C.F.R. § 314.127(a)(3)(i).

The statute further requires ANDAs to demonstrate the purported generic product's bioequivalence to a previously approved drug. 21 U.S.C. § 355(j)(2)(A)(iv); 21 U.S.C. § 355(j)(4)(F). That requirement is intended to ensure that every approved generic drug product is as safe and effective as the reference listed drug upon which its approval is based. For injectable small-molecule drugs, the bioequivalence requirement is typically satisfied by proving the chemical sameness of the active ingredient; FDA regulations provide for a waiver of *in vivo* bioequivalence and bioavailability requirements where the injectable product "contains *the same* active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application." 21 C.F.R. § 320.22(b)(1) (emphasis added). Thus, when a manufacturer cannot demonstrate that the purported generic contains the same active ingredients in the same concentrations as the reference drug, full proof of bioequivalence must be provided in the ANDA before the new drug can be approved.

### **III. Summary of the Argument**

FDA does not have authority to approve an ANDA unless the applicant demonstrates that the active ingredient in the purported generic is the same as that in the RLD. The unique complexity of Copaxone® makes such a demonstration impossible. Unlike most small-molecule drugs, the active ingredient in Copaxone®—glatiramer acetate—is a complex mixture of polypeptides that contains a huge, perhaps incalculable number of epitopes. At this time, even the most sophisticated chemical analytical tests, including multidimensional analysis, cannot

identify and characterize each of the active amino acid sequences that make up glatiramer acetate.

The fact that Copaxone®'s mechanism of action is not well understood further complicates matters. Although the drug produces multiple effects on the immune system, the mechanism by which it produces those effects are not clear. As a result, there would be no way to "back-test" the active polypeptide sequences in Copaxone® to determine which of them is responsible for the product's clinical efficacy even if the current state of the art could isolate and identify each of the amino acid sequences that make up the active ingredient in Copaxone®. Given these difficulties in characterizing the clinically active epitopes in glatiramer acetate, no applicant can demonstrate that their purported generic has the same active ingredient as Copaxone®, and FDA therefore cannot accept for filing or approve an ANDA based on Copaxone® as the RLD.

Applicants filing under 505(b)(2) and seeking to rely on studies conducted by innovators for proof of safety and efficacy also must show that the proposed follow-on product is sufficiently similar to the RLD to justify reliance on that data. Setting aside the inherent difficulty of proving that a purported follow-on product is similar to a drug that remains as uncharacterized as Copaxone®, there is no sound basis for approving a follow-on glatiramoid product based on the safety and efficacy data related to Copaxone®. As Teva has demonstrated through years of experiments, even minor changes in Copaxone®'s polypeptide mixture can result in significant clinical differences in safety and efficacy. As a result, the only method for showing that differences in the polypeptide mixture of a follow-on product are not significant is

through adequate, well-controlled pre-clinical and clinical trials. Because a new glatiramoid product cannot be shown to be the same, an AB therapeutic rating should also not be granted.

#### **IV. Argument**

##### **A. FDA Cannot Approve Any ANDA Citing Copaxone® as the RLD Because Current Chemical Analytical Techniques are Incapable of Showing that the Active Polypeptide Sequences in the Purported Generic are the Same as Those in Copaxone®**

###### **1. *It Is Not Possible to Demonstrate That a Purported Generic Version of Glatiramer Acetate Contains the Same Active Epitopes As Copaxone®***

Section 505(j)(2)(A)(ii)(II) of the FDCA (21 U.S.C. § 355(j)(2)(A)(ii)(I)) provides that FDA may not approve an ANDA unless the ANDA contains “information that the active ingredient of the new drug is *the same as* that of the listed drug” (emphasis added). FDA regulations make clear that “the term ‘same as’ means identical in active ingredients.” That rigorous standard cannot be met here.

As set forth above, the active ingredient in Copaxone®—glatiramer acetate—comprises a huge, perhaps incalculable number of epitopes. To determine which of these epitopes are active, and thus responsible for Copaxone®’s positive clinical effects in patients with RRMS, one would need to separate and then sequence the amino acids that comprise each epitope. Then, a sufficient quantity of each such molecular entity would have to be synthesized and screened for activity. Because there are no known surrogate markers for efficacy, such screening would not eliminate the need for both pre-clinical and clinical testing of each individual molecular entity.

These steps have never been taken, however, because the task is impossible. Current analytical chemistry methods are incapable of separating all of the potentially active ingredients in glatiramer acetate, since Copaxone® contains a huge, perhaps incalculable number of variable patterns in its active amino acid sequences. Many of these peptide species are highly similar in size, charge, and hydrophobicity, making separation of them even more difficult. Even state-of-the-art separation methods, including multidimensional methods combined with mass spectrometry, do not have the ability to discriminate among and separate the peptide sequences in such a complex mixture. Consequently, based upon the limitations of currently available, state-of-the-art analytical methods, it is not possible to fully characterize the active amino acid sequences in Copaxone®, and therefore, it is impossible for a purported generic glatiramer acetate product to demonstrate that its active epitopes are truly identical to those in Copaxone®'s active ingredient.

We are not aware of any prior case in which FDA has approved an ANDA referencing an incompletely characterized drug such as Copaxone®, in which the incompletely characterized elements of the product are of clinical significance. The Agency's experience with Premarin® is particularly instructive. In that case, FDA determined that proposed generic Premarin® product could not be approved through the ANDA process because the reference listed drug's active moieties were neither "definitively identified," nor "sufficiently well defined to permit an ANDA applicant to establish that a synthetic generic form...has the same active ingredients..."<sup>42</sup> That is

---

<sup>42</sup> Center for Drug Evaluation and Research. Department of Health and Human Services, Public Health Service, Food and Drug Administration. Approvability of a Synthetic Generic Version of Premarin. Memorandum to Douglas L Sporn, Director, Office of Generic Drugs. May 5, 1997.

precisely the case here. As with Premarin®, Copaxone®'s pharmacologically active epitopes have not been (and, using current analytical methods, cannot be) definitively identified, rendering it impossible for ANDA applicants to demonstrate that their proposed generic products have the same clinically active ingredients as Copaxone®. *See, e.g.*, Premarin® Rejection Letter (holding that ANDAs could not be approved for Premarin® on the ground that "Premarin is not adequately characterized and that, therefore, at this time, its active ingredients cannot be fully determined."). If anything, that principle is even more compelling in this case, since Copaxone® contains a far greater number of potentially active moieties than Premarin®, and current analytical techniques are not able to separate, identify, and test Copaxone®'s active moieties. Following the rule established in the Premarin® case, no ANDA referencing Copaxone® can be approved or accepted for filing.

The Agency's treatment of generic menotropins does not dictate a different result. *See Serono Labs. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (menotropins). In that case, FDA did hold that minor variations in a generic product's chemical composition did not strictly bar an approval of an ANDA. But FDA reached that conclusion in the menotropins case *only* because it was able to determine that slight variations in the naturally occurring isoforms of the menotropin carbohydrate side chains had ***no clinical significance***, based in part on results of prior clinical tests. *See id.* In addition, the active ingredient of the RLD was both well known and well characterized. The only issue presented in that case was whether the naturally occurring variations in the product's glycosylation—variations that were present in both the RLD and the generic—precluded approval of an ANDA. Because the same variations were present in the RLD and the proposed generic, and given prior clinical studies demonstrating a lack of clinical

significance from those variations, it was clear that there was no clinical significance to the variations.

Again, that is simply not the case here. Copaxone®'s active epitopes remain uncharacterized, and variations in the product's active polypeptide sequences are directly related to the product's clinical efficacy. An ANDA applicant cannot demonstrate "sameness" between a purported generic Copaxone®-like drug and Copaxone® using simple physicochemical comparisons—for example, by showing that its drug has the same average molecular weight and ratios of amino acids such as Copaxone®. Glatiramer acetate has a characteristic distribution of molecular weights; so a proposed generic's average molecular weight (MW) is not sufficiently informative. And because the lengths of the polypeptides in glatiramer acetate are a critical component of a drug's clinical efficacy, characterizing the distribution of MW within the mixture is essential. In short, the issue is not whether there are slight, clinically insignificant variations in the known active ingredient that would bar the approval of an ANDA. It is whether an ANDA filer can show that the active epitopes in Copaxone® are present at all, and whether they are present in the same amounts. Until those active moieties are isolated and identified, no ANDA filer can make the necessary showing that their product contains the same active ingredient.

If FDA nonetheless accepts an ANDA for generic glatiramer acetate despite the fact that Copaxone® pharmacologically active moieties remain uncharacterized and despite the fact that such a lack of characterization precludes the ANDA's sponsor from demonstrating that the active ingredient in its purported generic product is identical to that in Copaxone®, the Agency must at the very least ensure that the generic product shares each of the product's known characteristics,

including: (1) its specific molecular weight distribution profile; (2) the complex reproducible patterns in its amino acid sequence; (3) a characteristic ratio of molecules with C-terminal carboxylates to diethylamides; (4) a characteristic electrophoretic profile; (5) its specific hydrophobic interactions due to unique charge dispersion; (6) a specific proteolytic digestion profile; (7) a specific affinity to glatiramer acetate antibodies; and (8) a specific potency as determined by its biorecognition by glatiramer acetate-specific T cells. Each of these characteristics is directly associated with the product's clinical efficacy, and any putative generic glatiramer acetate product therefore must demonstrate that its drug is "identical" to Teva's glatiramer acetate product along each of these vectors, using techniques at least as sensitive and specific as those used for the glatiramer acetate in Teva's Copaxone®. However, we wish to be clear that even a drug which shares these characteristics with Copaxone® is not necessarily "the same as" Copaxone®, and in our view, is not suitable for approval as an ANDA.

In addition, Teva has developed a unique method of measuring MW distribution based on the separation of glatiramer acetate polypeptides, and calculates the product's MW distribution using a calibration curve generated from a set of well-characterized proprietary polypeptide markers. Unless an ANDA applicant for generic glatiramer acetate uses equally well-validated and scientifically meaningful tests, it cannot possibly ensure that the generic product's complex amino acid sequences and polypeptide lengths are chemically identical to Copaxone® and, thus, that the generic product will produce the same clinical results as Copaxone®. At the very least, then, FDA cannot approve a purported generic version of Copaxone® that does not share these characteristics as established by such well-validated tests, because such products demonstrably are not "the same as" Copaxone® and may well present serious safety and efficacy concerns.

## 2. *Biological and Immunological “Sameness”*

Even if purported generic glatiramer acetate products did share “the same” clinically significant molecular weight distribution and other attributes of the glatiramer acetate in Teva’s Copaxone®, chemical analysis would be only the first in a series of tests necessary to establish the “sameness” of a purported generic glatiramer acetate product. Immunological and biological tests of purported generic glatiramer acetate batches must be performed to demonstrate: (1) the consistency of the antigenic determinants in different batches; and (2) correlations among the immunoreactivity, chemical properties, and *in vivo* and *in vitro* biological activity of the drug. Such tests are the only way to ensure consistent biological activity of glatiramoid products on a batch-to-batch basis.

To that end, Teva performs extensive *in vivo* tests of Copaxone®’s biological activity as part of its stringent acceptance criteria for Copaxone® batches. Since glatiramer acetate’s biological activity is based on its cross-reactivity with MBP, Teva employs a validated EAE-blocking test to determine the consistency of Copaxone®’s biological activity. Results of this test demonstrate that Teva’s Copaxone® is reproducible on a batch-to-batch basis, ensure that each released Copaxone® batch is biologically active in a relevant disease model, and provide evidence that Teva’s Copaxone® batches are safe—that is, that they do not produce encephalitogenic activity. As a result of Teva’s strictly controlled manufacturing processes, no Copaxone® batch has ever shown any encephalitogenic activity and there is no evidence of immune activation by Copaxone® related to encephalogenicity. However, the EAE blocking test

has not been validated to demonstrate the clinical efficacy of glatiramer acetate or to serve as a substitute for clinical studies.

Because Copaxone® modifies pathological immune function, any ANDA applicant pursuing a purported generic glatiramer acetate product must likewise demonstrate immunological sameness to Copaxone® to establish the product's safety and efficacy. While Teva has mastered the production of Copaxone® over decades of research and experimentation, the cross-reactivity between glatiramer acetate and MBP raises inherent scientific and safety issues and there is a risk that encephalitogenic sequences may reside within glatiramoid mixtures manufactured by processes that differ from those perfected by Teva.

Teva further ensures the lack of encephalitogenic activity of Copaxone® by using a tightly controlled manufacturing process and an extensive battery of in-process and finished product tests. Over time, Teva has demonstrated the lack of encephalitogenic activity of Copaxone® using many other *in vitro* and *in vivo* models, in pre-clinical safety studies, in clinical trials with MS patients, and post-marketing studies of thousands of patients treated daily with Copaxone®. Unless an ANDA applicant can demonstrate the same consistent lack of encephalitogenic activity on a batch-to-batch basis, however, FDA should not and cannot approve its ANDA.

**3. *Clinical Testing Is Necessary to Demonstrate the Safety and Efficacy of a Purported Generic Glatiramer Acetate Product***

The safety, efficacy and lack of encephalitogenic potential of a purported generic glatiramer acetate product produced by a manufacturing process that differs from Teva's can be demonstrated only through pre-clinical studies and clinical safety and efficacy trials. Because glatiramer acetate cannot be fully characterized, manufacturing differences which create slight changes in the synthesis of glatiramer acetate can produce altered sequences of unknown safety and effectiveness. Process-related impurities (for example, aggregates formed due to intermolecular and intramolecular crosslinking or modified sequences) may have dramatic effects on product safety and efficacy.<sup>43</sup> Concerns over potential encephalitogenic activity, and questions of efficacy issues related to the product's immunological and biological characterization, cannot be addressed through *in vitro* tests and tests in animal models alone. Therefore, in addition to *in vitro* tests and other non-clinical tests, clinical trials to evaluate safety and clinical efficacy endpoints are the only meaningful way to establish safety and efficacy. Furthermore, because there are no validated surrogate markers of clinical efficacy of immunomodulator drugs for MS, only a clinical trial with relapse rate as the endpoint can definitively establish the clinical efficacy of a purported generic glatiramer acetate product in MS patients.

---

<sup>43</sup> Teva has submitted data to the Agency demonstrating that a product commercially available outside of the United States that purports to be glatiramer acetate has significant amounts of intermolecular and/or intramolecular crosslinks. The impact on the clinical safety and efficacy of such crosslinked structures, to the best of Teva's knowledge has not been established.

***d. Other Substances Purported to Be Glatiramer Acetate Fail Biological, Immunological, Analytical, and Safety Tests, Raising Concerns About the Demonstration of "Sameness"***

Finally, Teva is aware of substances purported to be glatiramer acetate; data show these substances fail biological, immunological, analytical, and safety and toxicity tests performed in the routine analysis of Copaxone®. Discriminatory chemical analytical methods unequivocally differentiate Copaxone® from these purported generic glatiramer acetate substances. As noted above, these products may indeed be members of the glatiramoid class of products. However, differences in the molecular weight distribution, formation of aggregates, changes in primary structure, as well as other more subtle differences within the class of glatiramoid products can have a significant and important impact on safety and effectiveness that can only be identified through appropriate clinical trials. Data from these products heighten concerns that such products are not the “same” as Copaxone®. Teva has submitted these data to the Agency as part of its correspondence to its NDA.

**B. Pharmacokinetic and Pharmacodynamic Tests Alone Are Insufficient to Demonstrate Bioequivalence and Bioavailability of a Generic Glatiramer Acetate Product**

***I. The Unique Mechanisms and Site of Action of Copaxone® Prevent the Use of Pharmacokinetic Studies to Establish Comparable Bioavailability With Other Glatiramoids***

Pharmacokinetic (“PK”) properties are considered valid measures of bioavailability and bioequivalence based on the assumption that measuring the concentration of a drug or its metabolites in the systemic circulation reflects drug availability at the site of action. FDA regulations define bioavailability as “the rate and extent to which the active ingredient or active

moiety is absorbed from a drug product *and becomes available at the site of action.*” See 21 C.F.R. § 320.1(a) (emphasis added). Similarly, bioequivalence is defined as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives *becomes available at the site of drug action.*” See 21 C.F.R. § 320.1(e)(emphasis added).

Evidence of *in vivo* bioavailability and bioequivalence for an ANDA may be waived for a parenteral solution for injection only if it “contains *the same* active and inactive ingredients in the same concentration” as the reference drug. See 21 C.F.R. § 320.22(b) (emphasis added). Evidence of *in vivo* bioavailability and bioequivalence for an ANDA may also be waived if such a waiver is compatible with the protection of public health. See 21 C.F.R. § 320.22(e). In this case, as set forth above, it is not possible for an ANDA applicant to prove that its glatiramer acetate product truly is “*the same as*” Copaxone® without running full chemical, biological, immunological, and clinical tests, and unless and until the manufacturer successfully completes those tests, there is no basis for waiving *in vivo* bioavailability and bioequivalence requirements set forth in the statute and FDA regulations.

There is an additional reason for not waiving the requirement for proof of bioequivalence and bioavailability for purported generic Copaxone® products. As noted above, Copaxone® achieves its initial effect locally in the subcutis, and the immune response is secondarily manifested as a systemic distribution of activated glatiramer acetate-specific T cells. In animals, T cells produced in the periphery cross the blood-brain barrier and accumulate in the CNS. Animal data suggest that glatiramer acetate-specific T cells in the brain modulate pathological

processes of MS through expression of anti-inflammatory cytokines and neurotrophic factors.<sup>44</sup> Therefore, studies measuring concentrations of Copaxone® or its metabolites in plasma are not informative as to drug availability at the site of action, and more importantly, are not indicative of drug activity. As a result, such studies would not meet specifications for establishing bioavailability or bioequivalence as defined by FDA regulations.

It also bears emphasis that a substantial fraction of the therapeutic glatiramer acetate dose is metabolized locally. Since glatiramer acetate is a heterogenous mixture of synthetic polypeptides, it is possible that multiple, chemically distinct, pharmacologically active polypeptide chains could be hydrolyzed at the site of action into smaller, chemically identical metabolites that could circulate systemically. Moreover, if aggregates are formed, they may be hydrolyzed in a different manner producing different metabolites and consequently different sequences will be presented. However, due to the local site of action, the pharmacological activity of glatiramer acetate is a function of the chemically distinct precursor polypeptide sequences in the periphery – not the chemically identical hydrolysis or metabolite products circulating in plasma. Therefore, even if Copaxone® and a purported generic glatiramer acetate produced the same plasma concentrations of each metabolite, it would not be sufficient to ensure that the immune cells at the site of injection are exposed to the same active polypeptide sequences. This inherent lack of specificity of plasma drug/metabolite level measurements is another reason why traditional PK studies measuring concentrations of glatiramer acetate or its metabolites in plasma are neither informative as to drug availability at the site of action, nor

---

<sup>44</sup> Aharoni *et al* (2003).

indicative of drug activity or safety.

Another obstacle to gathering useful PK data is a lack of adequate bioanalytical technology. Currently, “state-of-the-art” instrumentation is not capable of identifying all of the Copaxone® precursor polypeptides (original sequences) or metabolites, rendering typical PK data virtually meaningless.

Again, given the limitations of state-of-the-art analytical methodology, it is not possible for a purported generic to establish that its active ingredient is “the same as” that of Copaxone®. Consequently, a waiver of *in vivo* bioequivalence requirements is neither scientifically justified nor in conformance with FDA regulatory requirements. Moreover, a waiver of *in vivo* bioequivalence requirements is not compatible with the protection of public health.

## **2. *Pharmacodynamic Parameters Have Not Been Validated to Serve As Markers of Bioavailability or Bioequivalence***

When PK testing is not informative, surrogate measures, for example, the pharmacodynamic (“PD”) effects of the drug, may be sought to establish bioavailability or bioequivalence. There are consistent PD effects associated with Copaxone® administration. All MS patients treated with Copaxone® develop glatiramer acetate-reactive antibodies; concentrations of these antibodies peak at approximately 3 to 6 months after initiation of treatment, decrease beginning at approximately 12 months, and remain low thereafter.<sup>45</sup>

---

<sup>45</sup> Brenner *et al* (2001).

Additionally, Copaxone® polypeptides stimulate peripheral blood lymphocytes (“PBLs”) in MS patients and in healthy donors. Upon repeated exposure to Copaxone®, the specific proliferative response of PBLs decrease, and glatiramer acetate-specific T cells shift from a TH1 to a TH2 phenotype. These PD parameters have not been validated to serve as markers of bioavailability of Copaxone®, or as markers of bioequivalence between Copaxone® and other purported generic glatiramer acetate products.

More importantly, evidence of immunoavailability (development of anti-glatiramer acetate antibodies) or of an immune response (proliferation of glatiramer acetate-specific T cells) does not necessarily correlate with clinical efficacy. There appears to be a cascade of events after subcutaneous injection of Copaxone® that leads to clinical efficacy; antibody formation and proliferation of PBLs are early steps in the cascade but no correlation between these steps and clinical efficacy has been established. Moreover, any subtle shifts in the sequence of glatiramer acetate polypeptides can lead to immunological responses that could alter the safety and efficacy of the drug (for example, to the development of neutralizing antibodies). Such antibodies could block the efficacy of the approved dose, requiring higher dosing levels of the generic product to achieve the same level of immunopotentiation.

**C. FDA Should Not Approve Any 505(b)(2) Application Which References Copaxone® as the RLD Unless the 505(b)(2) Applicant Conducts Non-clinical Studies as well as Clinical Safety and Effectiveness Studies In RRMS Patients.**

Teva’s experience with TV-5010 demonstrates that even the most minor changes in the manufacturing of glatiramer acetate—and in the molecular weight distribution of the resulting product—will produce a new molecular entity with a significantly different potency and safety

and efficacy profile. Due to the complex nature of glatiramer acetate, any product that cannot be shown to be both a pharmaceutical and therapeutic equivalent of Copaxone® should be subjected to both non-clinical as well as clinical studies in RRMS patients. As described above, minor differences in either the manufacturing process or the active pharmaceutical ingredient (“API”) can produce altered polypeptide sequences, which are likely to affect the safety and efficacy of the product. Critical safety concerns, including potential encephalitogenic activity, and efficacy issues related to immunological and biological characterization, cannot be addressed through *in vitro* tests and tests in animals models alone, and therefore can only be addressed through clinical testing of the new product using clinical measures (reduction of relapse rate as well as a comparable safety profile). Therefore, any product which references Copaxone® should be required to conduct both pre-clinical and clinical studies to ensure its safety and efficacy in both naive patients and those patients previously treated with Copaxone®.

Specifically, FDA should require the applicant to conduct clinical studies in RRMS patients which are adequately powered to demonstrate safety and efficacy. MS is a life-altering and irreversible disease in which there is neither any guarantee, nor any clinical evidence that once neurological damage is sustained, that damage can be repaired or reversed. Given that an ineffective or unsafe product can lead to unalterable damage, the manufacture, chemical composition, and clinical activity of such a product warrants rigorous scrutiny which only can be provided by clinical testing. FDA should require clinical studies comparable in size and duration to those for any NME. Moreover, given the difficulty of demonstrating efficacy in the MS population, a minimum two-year duration for clinical trials is necessary to satisfy the statutory requirements for “substantial evidence” of efficacy with an active comparator and placebo

control as a reference arm. *See* 21 U.S.C. § 355(d). Therefore, any product submitted as a 505(b)(1) or a 505(b)(2) application, should be required to conduct clinical studies which meet the above stated requirements.

**V. Conclusion**

For the foregoing reasons, Teva requests that FDA not approve nor accept for filing any additional ANDA or 505(b)(2) applications for a purported generic glatiramer acetate product until and unless the standards set forth in this Petition are met.

**VI. Required Material**

**A. Environmental Impact**

Petitioner believes that this petition does not require an environmental impact analysis report under 21 C.F.R. § 25.1(g) (1995).

**B. Economic Impact**

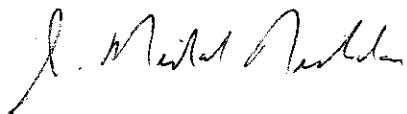
An economic impact report is required only when requested by the Administration and such report has not been requested. 21 C.F.R. § 10.30(b).

**CERTIFICATION**

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to me on or about the following dates, July, 2004 through September 2008. The information contained in this petition has been shared with the FDA on numerous occasions from 2004 to the present date and requests for meetings with the Agency to discuss this important information have been denied.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, Teva. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



J. Michael Nicholas, Ph.D.,  
Sr. Director, Strategic Regulatory Affairs

Cc: Janet Woodcock, Director, Center for Drug Evaluation and Research  
Russell G. Katz, M.D., Director, Division of Neuropharmacological Drug Products  
Gary J. Buehler, R.Ph., Director, Office of Generic Drugs  
Steven D. Silverman, Esq., Director, New Drugs and Labeling Compliance